REMARKS

Claims 1-88 are pending in the application. Claims 43, 54, 67-69, and 77-88 are withdrawn from consideration and Claims 1-42, 44-53, 55-66, and 70-76 have been examined. Claims 1-42, 44-53, 55-66, and 70-76 stand rejected. Claims 1, 21, 22, 44, 57, 63, 65, and 70 have been amended. No new matter has been added. Applicants respectfully request reconsideration and allowance of Claims 1-42, 44-53, 55-66, and 70-76.

The Rejection of Claims Under 35 U.S.C. § 102(e)

The Examiner has rejected Claims 1-42, 44-53, 55-66, and 70-76 under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 5,741,899 (Capon et al.). According to the Examiner, Capon et al. provides an enabling disclosure for making and using the vectors and cells for obtaining drug-induced proliferation of primary cells. Applicants respectfully disagree.

Claims 1-42, 44-53, 55-66, and 70-76 are directed to primary hematopoietic cells, specifically primary hematopoietic stem cells, and methods of making and using these cells, wherein the cells express fusion proteins comprising at least one drug binding domain and at least one signaling domain, which render the cells sensitive to drug-induced growth, proliferation, or differentiation. In order to more distinctly point out the invention, Claims 1, 21, 22, 44, 55, 57, 63, 65, and 70, from which Claims 2-20, 23-43, 45-52, 58-62, 64-66, and 71-76 depend, have been amended to recite that exposure of the cells to the drug reversibly induces growth, proliferation, or differentiation. For the following reasons, applicants submit that Capon et al. does not provide an enabling disclosure of the claimed invention.

First, Capon et al. does not provide an enabling disclosure for making and using primary hematopoietic cells containing a construct encoding a fusion protein comprising at least one signaling domain and at least one drug-binding domain. All the fusion proteins explicitly described in Capon et al. that contain a domain capable of binding to a drug include this

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CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

$(FKBP)_3$ cassette, which consists of 3 repeats of an FK506 binding protein module (see Col. 35, lines 6-9, lines 18-21, lines 28-31, lines 38-41, lines 51-54, lines 61-64, and Col. 36, lines 4-7). The Inventor's Declaration submitted herewith (hereinafter "Blau Declaration") establishes at paragraph 6 that constructs that contain repetitive sequences, such as multiple copies of an FKPB domain, have a high frequency of recombination when introduced into cells using retroviral vectors, which very likely would compromise the function of the introduced sequences (see, e.g., Thomis et al. (2001) *Blood* 97(5):1249-1257, page 1251, Col. 1). For this reason, the fusion proteins of Capon et al. including the $(FKBP)_3$ cassette would not be correctly synthesized and would therefore be nonfunctional when introduced into cells using retroviral vectors (see Blau Declaration, paragraph 6). At the time of filing the application that issued as the Capon et al. patent (June 7, 1995), the only method for achieving stable gene delivery into primary hematopoietic cells was by using retroviral vectors (see Blau Declaration, paragraph 7). Therefore, Capon et al. does not provide an enabling disclosure for making and using primary hematopoietic cells (*e.g.*, primary hematopoietic stem cells) containing a construct encoding a fusion protein comprising at least one signaling domain and at least one drug-binding domain (see Blau Declaration, paragraph 7).

Second, Capon et al. does not provide an enabling description of methods of expanding primary hematopoietic cells or methods of treating a hemopoietic disease or condition by exposing cells containing a construct coding for a fusion protein comprising at least one signaling domain and at least one drug-binding domain to the drug. Capon et al. describes placing CPR-expressing $CD8^+$ T cells in "culture dishes coated with saturating concentrations of either OKT4A, anti-human Fc Mab, gp120, gp160-expressing cells, gp41/gp120-expressing cells, HIV-1 infected cells or FK1012" (Col. 42, lines 61-64). This would not lead to drug-induced proliferation of primary hematopoietic cells because coating the culture dishes with the

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CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

drug (FK1012) would impede or prevent diffusion of the drug (see Blau Declaration, paragraph 8). Moreover, saturating concentrations of FK1012 have been shown to inhibit growth by occupying all of the FKBP sites, thereby preventing dimerization (see, e.g., Blau et al. (1997) *Proc. Natl. Acad. Sci. U.S.A.* 94:3076-81, page 3078, Col. 1; Blau Declaration, paragraph 8). Therefore, the disclosure of Capon et al. does not enable a person of skill in the art practice, without undue experimentation, methods of expanding primary hematopoietic cells, including primary hematopoietic stem cells, or methods of treating a hemopoietic disease or condition by exposing to a drug cells containing a construct coding for a fusion protein comprising at least one signaling domain and at least one drug-binding domain.

Third, Capon et al. does not describe or suggest reversible induction of cell proliferation. To the contrary, Capon et al. suggests the use of genes additional to the CPR-encoding gene, such as the thymidine kinase or cytosine deaminase genes, or the multi-drug resistance gene, to increase or decrease the number of cells expressing CPRs (Capon et al., Col. 22, lines 2-19; Blau Declaration, paragraph 10). Thus, Capon et al. did not contemplate that a small molecule inducer, such as FK1012, could be used to conditionally regulate the growth of genetically modified primary cells.

For the reasons described above, applicants submit that Capon et al. does not disclose or suggest the claimed invention and respectfully request withdrawal of this ground of rejection.

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CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

CONCLUSION

In view of the foregoing amendments and remarks, Claims 1-42, 44-53, 55-66, and 70-76 are believed to be in condition for allowance. If any issues remain that can be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicants' attorney at 206.695.1783.

Respectfully submitted,

CHRISTENSEN O'CONNOR
JOHNSON KINDNESS[PLLC]

Karen Blöchlinger, Ph.D.
Registration No. 41,395
Direct Dial No. 206.695.1783

Enclosures:
Inventor's Declaration Under 37 C.F.R. § 1.132
Curriculum Vitae of Carl Anthony Blau

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LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS[PLLC]
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100